of patients achieved CR and the 1-year OS in this group was 43%.

Conclusion: The 5-azacitidine is a treatment modality that can improve or stabilize the disease, allowing time for patients to reach alloHCT, with little toxicity, and can induce response after post-alloHCT relapses.

379

Monitoring Changes in Serum Albumin (SA) Concentrations As an Early and Objective Indicator of Potential CMX001-Associated Gastrointestinal (GI) Adverse Drug Effects

Herve Mommeja-Marin [1], Thomas M. Brundage [2], Dorothy J. Margolskee [2]. [1] Medical / Clinical, Chimerix, Inc., Durham, NC; [2] Chimerix

Background: CMX001 is an orally bioavailable, broad spectrum, lipid acyclic nucleoside phosphonate converted inside cells to the active antiviral, cidofovir diphosphate. In the preclinical toxicology program, GI AEs (diagnosed as gastropathy and enteropathy; dose-related changes included flattening or loss of epithelial cells lining the lumen of the small intestine on chronic dosing) were dose-limiting after daily administration; however, there were no GI AEs or gross/microscopic gut changes when animals were dosed twice-weekly (BIW) up to 9 months. Radiolabel studies in mice confirmed that CMX001 concentrates in the gut mucosa more than in other tissues. In a Phase 2 dose-escalation study (CMX001-201; ClinicalTrials.gov identifier: NCT00942305) evaluating CMX001 for CMV prophylaxis in allogeneic hematopoietic stem cell transplant (HSCT) recipients, an increased rate of profuse watery diarrhea was seen at 200 mg BIW and was considered dose-limiting in this population. A program-wide safety monitoring and management plan that included an option for dose interruption ($\leq$ 2 weeks) in subjects with $\geq$ Grade 3 diarrhea was introduced. Subsequently, few subjects ($\leq$ 10%) discontinued therapy because of GI AEs, indicating that dose interruption is an appropriate strategy to manage CMX001-associated GI AEs and to achieve effective CMV suppression in this population.

Methods: Serum chemistry data were evaluated for changes in SA, a well-established marker of protein loss, to assess the potential relationship to diarrhea. Abnormally low SA concentrations were tabulated and the lowest value identified through +1 week post treatment. A clinically meaningful SA decrease was defined as value $\leq$ 30 g/L (lower limit of normal 33 g/L) and $\geq$ 4 g/L lower than baseline.

Results: Increased grade and/or duration of diarrhea correlated with the decrease in SA concentrations over time as shown in the Kaplan-Meier plots with data grouped by "low" ($\leq$ 100 mg/week) and "high" ($\geq$ 200 mg/week) CMX001 dose vs. placebo. To rule out GI-GVHD (a common cause of diarrhea in HSCT recipients), the SA data from solid organ transplant (SOT) patients treated with CMX001 in an expanded access study (CMX001-350; ClinicalTrials.gov ID: NCT01143181) were also evaluated. A similar timing of decrease in SA concentrations was seen in these subjects who are unlikely to have GVHD; urinalysis data also excluded proteinuria as a cause.

Conclusions: Our clinical experience in the HSCT population is consistent with preclinical findings. On chronic dosing, CMX001 likely accumulates in the gut mucosa in some patients and causes diarrhea that may be more pronounced in individuals with other causes of diarrhea (eg, GI-GVHD). Dose interruption gives the gut mucosa time to recover, allowing subjects the opportunity to resume therapy. Monitoring SA changes in patients may provide an early and objective indicator of potential drug-related GI AEs.

380

Renal Safety of Broad Spectrum Antiviral CMX001 in the Prevention of CMV Infection Post- Allogeneic Hematopoietic Cell Transplantation (HCT)

Herve Mommeja-Marin [1], Thomas M. Brundage [2], Dorothy J. Margolskee [2]. [1] Medical / Clinical, Chimerix, Inc., Durham, NC; [2] Chimerix

Background: CMX001 is an orally bioavailable, broad spectrum, lipid acyclic nucleoside phosphonate converted intracellularly into the active antiviral, cidofovir diphosphate. Unlike cidofovir, CMX001 is not a substrate for the anion organic transporter and therefore is not concentrated in the kidney.

Methods: Study CMX001-201 was a 9-11 week randomized, placebo-controlled, double-blind, dose-escalation study (evaluating 40 mg weekly [QW], 100 mg QW, 200 mg QW, 200 mg twice-weekly [BIW] and 100 mg BIW) of CMX001 for the prevention of CMV infection post-HCT (ClinicalTrials.gov ID: NCT00942305). Treatment was initiated at the time of engraftment and continued until Week 13 post-HCT. Results presented elsewhere have shown that CMX001, at various doses, was active and well tolerated in the prevention of CMV infection or disease. Renal safety was assessed throughout the duration of therapy using serum creatinine, urinalysis and estimated glomerular filtration rate (GFR, MDRD4 formula).

Results: 230 subjects were enrolled in the study; 59 received placebo and 171 received CMX001 at various doses. 24 subjects (41%) on placebo and 77 subjects on CMX001 (45%) had BK viruria prior to dosing. One subject discontinued CMX001 40 mg QW due to acute renal failure; no other subject discontinued from the study due to renal adverse events. Results of calculated GFR by Study Cohort and over time are presented in Table 1 below. Overall, renal function tended to decline in placebo recipients while renal function appeared to improve in subjects who received CMX001 at 200 mg per week (either QW or divided into 2 BIW doses). The renal function decline in placebo recipients appeared to be associated by the presence of BK virus (BKV) in the urine at the time of treatment commencement, while the proportion of subjects with renal dysfunction was similar between BKV positive and negative subjects among CMX001 recipients. There was also a decreased incidence of microscopic hematuria in BKV infected subjects treated with CMX001 as compared to placebo recipients (6% vs. 25%).

Conclusions: CMX001 when administered at doses of 200 mg per week is not associated with signs of nephrotoxicity

Table 1
Study 201: Mean (N) Change from Baseline in GFR (mL/min/1.73m^2) by Visit and Dose

Visit	Placebo	CMX001 40 mg QW	CMX001 100 mg QW	CMX001 200 mg QW	CMX001 100 mg BIW
Week 2	-6.5 (56)	-7.7 (23)	-11.6 (26)	-9.5 (37)	-4.5 (49)
Week 4	-8.7 (46)	-9.4 (19)	-8.6 (25)	-12.4 (31)	-3.3 (44)
Week 6	-10.1 (35)	-7.0 (13)	-12.0 (22)	-1.9 (24)	1.3 (33)
Week 8	-18.5 (36)	-2.2 (12)	-11.3 (19)	5.8 (18)	12.2 (31)*
Week 10	-15.4 (21)	-7.3 (5)	-15.6 (13)	5.7 (14)	6.1 (21)*
Post-Week 1	-13.3 (57)	-5.8 (19)	-2.8 (25)	8.8 (35)	7.7 (49)*

* $P < 0.05$ t-test versus placebo

and may mitigate the effect of BKV infection post-HCT. Further studies are warranted to assess the effect of CMX001 on BKV infection and its association with improved renal function.

381

The Management of Relapsed AML or MDS Following a T-Cell Depleted Allogeneic Stem Cell Transplant

Ewelina Morawa [1], Emily Zabor [2], Molly Maloy [1], Sean Devlin [2], Sergio A. Giralt [1]. [1] Memorial Sloan-Kettering Cancer Center, New York, NY; [2] Department of Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Relapse is a major cause of treatment failure of allogeneic stem cell transplant (SCT) for AML. Most retrospective analyses describing the natural history of relapse have not included recipients of T-cell depleted transplants (TCD). We hypothesized that response to therapy may be different in recipients of TCD-SCT and that they may be more amenable to graft versus leukemia effects. Thus we performed a retrospective analysis of our patients who relapsed after a TCD-SCT.

Materials and Methods: From 2003 until 2012 we identified 42 patients with AML or MDS who relapsed after a TCD-SCT at MSKCC. Patients were divided into four groups based on management of relapse: supportive care (n=7), chemotherapy only (n=17), chemotherapy plus DLI (n=8), and chemotherapy plus 2nd SCT (n=10). Patient and disease characteristics were compared across the four groups using Fisher's exact test when categorical and the Kruskal-Wallis test when continuous. Kaplan-Meier methods were used to estimate survival probabilities and the log-rank test evaluated differences in survival between groups. Of the 10 patients who underwent a second HSCT, 8 received T-cell replete and 2 underwent another TCD-SCT.

Results: Across groups, there were no significant differences in sex ($P = .086$), donor type (related vs unrelated;$P = .082$), percentage of blasts on relapse (median 25%;$P = .317$), and all cause mortality ($P = .088$). There was a statistically significant difference in the age of patients ($P = .010$); youngest in the chemo plus 2nd SCT group (median 41.5 yrs). The median follow up time amongst survivors was 24.4 months (range, 13.6 - 69.8 m). There were 34 all cause mortality events; 4 due to NRM. Median survival for all groups was 16 months (95% CI, 11.8-27.1). At 12 month follow up, the probability of survival in supportive care, chemo only, chemo plus DLI, and chemo plus 2nd SCT group were 43%, 41%, 88%, and 70%, respectively. There was no statistically significant difference in overall survival (OS) between the groups ($P = .088$). Patients in the chemo plus DLI and chemo plus 2nd SCT groups had the longest median OS of 28.6 months and 20.2 months, respectively. The median survival of patients who received any salvage chemotherapy was 19.3 months (95% CI, 10.5-28.6) compared to 20.2 months (95% CI, 11.9-NA) for those receiving chemo plus 2nd SCT ($P = .180$). Complete remission was achieved at any time in 5 patients in chemo plus 2nd SCT, 3 patients in chemo plus DLI, and none of the patients in chemo only group ($P = .003$). Use of hypomethylating agents versus other salvage chemotherapy at any point in treatment did not improve OS ($P = .745$).

Conclusions: AML patients relapsing after a TCD-SCT can be successfully treated, however long term disease control is rare. Due to the small number of patients we were not able to demonstrate statistically significant difference in outcomes among different salvage strategies.

382

BK Virus by PCR From Peripheral Blood At Day 21 After Allogeneic Transplant Predicts Risk for Hemorrhagic Cystitis

Jaime Anne Hilger Mullin [1], Tatyana Sklyar [2], Sushil Ratnaparkhe [2], Tarik Hadid [1], Gina Berteotti [3], John Lister [3], Entezam Sahovic [3]. [1] Hematology and Oncology, Western Pennsylvania Cancer Institute, Pittsburgh, PA; [2] Internal Medicine, WPAHS, Pittsburgh, PA; [3] Western Pennsylvania Cancer Institute, Pittsburgh, PA

Introduction: Hemorrhagic Cystitis (HC) is a well-recognized complication of hematopoietic stem cell transplantation (HSCT) and is frequently associated with BK virus reactivation. While self-limited, it is associated with significant morbidity. We hypothesized that serum PCR testing for BK virus (BKV) before and after HSCT might predict development of HC. To test our hypothesis, we conducted a retrospective analysis of patients who underwent allogeneic HSCT from 2005 to 2012 at our institution.

Methods: We identified 162 patients who underwent allogeneic HSCT, 124 received myeloablative conditioning (MA) and 38 received reduced intensity conditioning (RIC). The MA regimen consisted of fludarabine 50 mg/m^2/day IV for 5 days and busulfan 3.2 mg/kg/day IV for 4 days with or without total body irradiation (TBI) of 200 cGy/day for 2 days (FB4 or FB4/TBI). The RIC regimen (FB2) consisted of fludarabine 30 mg/m^2/day IV for 5 days and busulfan 3.2 mg/kg/day IV for 2 days. Ninety-six patients received matched unrelated donor HSCT (MUD), 60 received matched related donor (MRD) and 6 received unrelated cord blood (UCB). Serum BKV screening was performed in 70 patients before HSCT and in 63 patients at day +21. Patients with urinary symptoms were tested for BKV in urine by PCR.

Results: Overall 36/162 patients (22%) developed HC. Twenty-six of the 36 (72%) were positive for BKV. The median time to development of HC from transplant was 37 days. The odds of developing HC was 4.2 fold higher in patients receiving MA conditioning as compared to RIC ($P = .01$; 95% CI=1.22-14.69). The severity of HC was not increased with the addition of TBI ($P = .8$). Graft source had no influence on the incidence of HC ($P = .6$). HC developed in 12/23 patients (52%) who were positive for BKV at day +21 and in only 4/40 patients (10%) who were negative. Patients who tested positive for BKV at day +21 were 9.8 times more likely to develop HC than those who tested negative ($P = .0005$; 95% CI =2.63-36.67). Testing at day +21 had a negative predictive value (NPV) of 90% ($p = < .0001$; 95% CI=76-97%).

Conclusion: HSCT using MA conditioning significantly increases the likelihood of developing HC compared to RIC. While pre-HSCT serum testing of BKV had no significant predictive value, testing at day +21 helped identify a cohort of patients at higher risk for development of HC. A clinical trial of antiviral pre-emptive therapy might be warranted for patients who test positive on day +21.

383

Impact of Iron Overload On Immune Function for Patients Undergoing Allogeneic Transplants for Hematologic Disorders: Results of Pilot Study

Seema Naik [1], Ralph D'Agostino Jr. [2], Mary Ann Knovich [3], David Grier [4], Robin Harrelson [5], Linda McPhail [6]. [1] Hematology and Oncology, Wake Forest Baptist Medical Center, Winston